

APPENDIX D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: William J. Rea, et al. Attorney Docket: 16715CPA
Serial No.: 08/902,692 Art Group Unit: 1644
Filed: July 30, 1997 Examiner: Schwadron, R., Ph.D.
For: AUTOGENOUS LYMPHATIC FACTOR FOR
MODIFICATION OF T AND B LYMPHOCYTE PARAMETERS

SUPPLEMENTAL

DECLARATION OF VERNON E. SCHOLES, Ph.D.

My name is Vernon E. Scholes. My residence is 1816 Cedar Bluffs Way, Las Vegas, Nevada 89128. I am over 21 years of age, of sound mind, and competent to make this Declaration.

All of the statements made in this Declaration made on personal knowledge are true or, if made on information and belief, are believed to be true.

Expert Qualifications and Experience

I earned a Ph.D. in Medical Microbiology at the University of Kansas, Lawrence, Kansas.

My qualifications and experience include having been a Professor of Microbiology and/or Immunology at several universities. I have taught courses in microbiology, immunology, cell biology, botany, virology, mycology, parasitology, and medical technology at undergraduate, graduate, medical, and dental schools. I have performed research in the areas of immunobiology (AIDS and cancer), virology, microbiology, and botany; have directed the research of 11 M.S. students, 10 Ph.D. students, and 4 Post-doctoral students; and have written and/or presented over 60 research papers, abstracts, and presentations. I have set up 2 flow cytometry laboratories and pioneered development of immunological and cell cycle analysis using the flow cytometer. In addition, I have been an invited participant in 7 conferences of the Society for Analytical Cytology. I continue to be an independent Immunology/Microbiology Consultant.

A true and correct copy of my latest curriculum vitae is attached hereto as Exhibit A.

A true and correct list of my "Publications, Presentations, and Abstracts," and "Special Symposia and Consultantships" and list of the M.S. Theses, Ph.D. Dissertations, and Post-Doctoral Works that I have directed is attached hereto as Exhibit B.

APPENDIX D: Brief for Appellants, U.S. Patent Application
Serial No. 08/902692 filed July 30, 1997
Inventors: William J. Rea and Bertie B. Griffiths

Scope of Review

Dr. Rea and Dr. Griffiths requested my independent review of their application for patent, which I understand was filed with the United States Patent and Trademark Office on July 30, 1997 and further identified as U.S. application serial number 08/902,692.

In particular, I was provided with a copy of the following papers from the application file history:

- a) application entitled "Autogenous Lymphocytic Factor for Modification of T and B Lymphocyte Parameters";
- b) an "Amendment" to the application dated April 7, 1999;
- c) a further "Preliminary Amendment" to the application dated December 20, 1999;
- d) a second "Preliminary Amendment" to the application dated September 11, 2000; and
- e) an "Office Action" dated September 29, 2000, together with the references cited against the application, Youdim et al. (Clinical Ecology, Volume 7, Number 3) and Warren (U.S. Patent No. 4,535,384).

I was requested to provide my independent expert opinion regarding the issues raised by these papers, including:

- a) the meaning of "normal" lymphocytes, in the context of how the term was used in the application;
- b) whether the invention as disclosed in the application requires any separation of "normal" lymphocytes from other lymphocytes prior to the propagation of the lymphocytes;
- c) whether Youdim et al. discloses any teaching or suggestion of making autologous lymphocytes factor (ALF); and
- d) whether Warren discloses any teaching or suggestion of propagating cells or making autologous lymphocytes factor (ALF); and
- e) whether the hypothetical combination of Youdim et al. and Warren would render obvious the general methods of Applicant's invention, as defined in Claim 49 and exemplified by the particular preparation steps set forth at pages 8-10 and the following treatment steps and clinical testing.

"Normal" Means Normal-Functioning Lymphocytes

"Normal" to a pathologist would more likely refer to normal-appearing or normal in appearance, whereas "normal", to an immunologist, like myself, would refer to normal-functioning lymphocytes. There is a great difference between normal in appearance and normal in function. Normal appearing lymphocytes to a pathologist may not be "normal" functioning lymphocytes. That is, a patient suffering from immune deregulation may have normal appearing but not normal functioning lymphocytes.

One example of immune deregulation is shown in the histogram analysis as described in the original submission of the invention. In DNA analysis, normal functioning lymphocytes would have approximately 90% of the lymphocytes in the G₀/G₁ phases of the cell cycle, as illustrated in Figure 1 and by representative sample DNA measurements of normal or control volunteers shown in Figures 2a and 2b of the application. In contrast, deregulated lymphocytes would tend have approximately 10-15% of the lymphocytes in the G₀/G₁ phases and 85-90% in the S/G₂M phases, as illustrated and best shown by the representative sample DNA measurements of environmentally compromised individuals shown in Figures 3a, 3b, and 3c, especially Figures 3b and 3c.

Furthermore, as used in the disclosure of the invention, the functioning of the lymphocytes, whether "normal" or deregulated, is analyzed using an aggregate of cells in a sample, not by looking at an individual cell.

The application itself indicated that "normal" refers to normal functioning cells. For example, the application refers to "the patient's own normal (non-cancerous or otherwise dysfunctional) lymphocytes. (Application, page 6, lines 9-10.) Perhaps it would have been better to state "normal functioning" lymphocytes rather than just "normal" in the body of the submission, however, in the full context of the disclosure, the use of the term "normal" is clearly directed to normal functioning cells, especially as would be indicated by DNA analysis.

No Separation of "Normal" Lymphocytes Prior to Propagation Is Required

According to the example of the preparation of ALF described at pages 8-10 of the application, there is no step of any separation of "normal" lymphocytes from abnormal or deregulated lymphocytes prior to the propagation step.

Furthermore, even in a patient suffering from immune deregulation, especially where environmental factors such as a chemical sensitivity contribute to the deregulation, at least some portion of the lymphocytic cells would be expected to be either normal functioning or capable of normal functioning under healthier conditions, i.e., when the incitant to the deregulation is removed. It should be understood from the context of the disclosure in the application, especially the lack of any separation step in the example, that, under culturing conditions, ideal for lymphocytic cell growth and propagation, normal functioning cells in the lymphocytic sample would be readily propagated. The purpose of the propagation step is to produce abundant numbers of robust, normal functioning lymphocyte cells from a patient's own normal lymphocyte cells that are either normal functioning or capable of normal functioning under healthier conditions.

Youdim et al. Does Not Disclose or Suggest Propagating Cells or Autologous Factor (ALF)

Youdim et al. does not disclose or suggest propagating or culturing cells to obtain abundant numbers of healthy lymphocytes. For example, the publication of Youdim et al. (pg. 56, line 4) notes that

the lymphocytes were "pooled" from random normal healthy donors (line 2). At the time of the Youdim publication, it was still a common practice in the art to use "pooled" lymphocytes, e.g., lymphocytes from a large number of donors in order to obtain sufficient numbers of lymphocytes from which to extract sufficient "transfer factor" (TF). Environmentally sensitive patients refers to the patient being treatment with TF, not the persons from which the TF was obtained. For example, Youdim specified "Peripheral blood from random normal health donors." There is no teaching or suggestion in Youdim that TF was produced from "autogenous blood cells." This is an important difference between Youdim et al. and the application of Drs. Griffiths and Rea, i.e., Youdim et al. used blood from random healthy donors. Griffiths and Rea used autogenous lymphocytes.

Warren Does Not Disclose or Suggest Propagating Cells or Autologous Factor (ALF)

Warren includes the statement "the incubation of the syringe and contents for 20 min. at 37° C" at column 2, lines 60-64. This "incubation" time of 20 minutes would not be for propagation of cells because the generation time of the cells would be approximately 20 hours or more. In fact, the "incubation" time of 20 min. at 37° C is to remove the macrophage type cells by giving them sufficient time to adhere to the "cotton wool" and not for propagation. This procedure for the removal of macrophage type cells is well known to those skilled in this art.

In contrast, the "propagation" of cells would be understood by a person of ordinary skill in the art to require sufficient generation time for the increase in the number of cells.

Also, in my more than 30 years practicing this art, I have never heard of using "cotton wool" for this procedure but instead using glass wool fibers as described by Warren in column 3, line 68. I fear Warren did not carefully edit his submission, since he states using "cotton wool" in column 2, lines 55-56, and glass wool in column 3, line 68.

Furthermore, Warren also taught the use of pooled lymphocytes from healthy donors. Warren's description of a "preferred embodiment" in which he described preparation of lymphocytes was on a "pilot plant scale" (as would be described in industrial language) and in column 3, lines 63-66 he described the preparation on a "production scale" (scale-up technique) thereby producing sufficient numbers of lymphocytes from which to extract TF in quantities sufficient to include in his composition for skin treatments. According to Warren's patent, a routineer would have to use large numbers of lymphocytes "prepared by utilizing 'scale-up techniques' of the procedure outlined above which permit purification of large numbers of lymphocytes" as described in column 3, lines 63-66. This is why Warren was so emphatic about using lymphocytes from suitable donors; i.e., donors having no history of recurring infection by herpes virus (Warren column 2, lines 35-37). (Of course, Warren's patent was filed April 30, 1982 prior to the AIDS epidemic.) Warren's method is different from that of Drs. Rea and Griffiths in that Warren used blood from healthy donors while Rea and Griffiths used autologous lymphocytes.

Invention Not Obvious Based on Hypothetical Combination of Youdim et al. and Warren

My understanding is that the claimed invention in the application of Rea and Griffiths is defined and illustrated by the following pending claim:

Claim 49: A method for treating a chemically sensitive individual comprising the steps of:

- (a) collecting a blood sample from the individual;
- (b) isolating mixed T and B lymphocytes from the blood sample;
- (c) propagating the isolated mixed T and B lymphocytes to obtain propagated lymphocytes;
- (d) lysing the propagated lymphocytes to obtain a lysate; and
- (e) administering the lysate to the individual.

In my opinion, these basic steps are fully supported by the written description and figures of the application, and should not be interpreted by a person of ordinary skill in the art to require any separation of "normal" lymphocytes from abnormal or deregulated lymphocytes prior to the propagation step.

Rea and Griffiths are using a technique of cell culture (propagation) of lymphocytes to produce sufficient numbers of normal functioning lymphocytes from which to extract quantities of ALF sufficient to use in replacement of insufficient concentrations of ALF in patients immunologically deregulated or replacement of ALF to stimulate an immunologically deregulated patient to proper regulation.

Based on the foregoing, in my opinion, the hypothetical combination of Youdim et al. and Warren does not teach or suggest the invention as defined by Claim 49 and as set forth in the written description of the invention, including the specific, illustrative example procedure set forth at pages 8-10 of the application and the following treatments steps and clinical testing.

I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Further Declarant sayeth not.


Vernon E. Scholes


Date

1816 Cedar Bluffs Way
Las Vegas, NV 89128

(702) 243-0319

EDUCATION

B. A., Biology, Phillips University, Enid, OK.
M.S., Microbiology, University of Oklahoma, Norman, OK.
Ph.D., Medical Microbiology, Univ. of Kansas, Lawrence, KS.

WORK HISTORY

- Adjunct instructor, microbiology, 1992 to present.
Community College of Southern Nevada, Las Vegas, NV.
- Microbiology/Immunology Consultant, 1988 to present.
- Clinical Asst. Professor, 1990 to present. Pathology
Dept., University of Nevada School of Medicine, Reno, NV.
- Immunology/Flow Cytometry consultant, 1989-91. Associated
Pathologists Laboratories, Las Vegas, NV.
- Special Assistant to President (Scientific Affairs),
1985-88. Imreg, Inc., New Orleans, La.
- Professor and Department Head, Microbiology and
Immunology, and Director of University Hospital
Microbiology/Immunology Clinical Laboratories, 1983-85.
University of the West Indies School of Medicine,
Kingston, Jamaica.
- Professor and Dept. Chairman, Microbiology/Immunology,
1977-83. Oral Roberts University Schools of Medicine and
Dentistry, Tulsa, OK.
- Professor and Dept. Chairman, Microbiology/Immunology,
1972-77. Univ. of South Alabama School of Medicine,
Mobile, AL.
- Professor, Microbiology, 1962-72. North Texas State
Univ., Denton, TX.
- Adjunct professor, Microbiology, 1968-70. Baylor
University School of Dentistry, Dallas, TX.
- Director of Laboratories, 1960-62. Missouri State Chest
Disease Hospital, Mt Vernon, MO.

EXPERIENCE

- Taught courses in microbiology, immunology, cell biology,
botany, general biology, virology, mycology, parasitology,
and medical technology in undergraduate, graduate,
medical, and dental schools.
- Performed research in the areas of immunobiology (AIDS and
cancer), virology, microbiology and botany.
- Set up and administrated microbiology/immunology
departments in 3 medical schools.
- Managed clinical and research microbiology/immunology
laboratories.
- Member of the Alabama State Board of Basic Science
Examiners (in place of National Board Examination, Part 1)

RESEARCH

- Research investigations in cellular immunology, virology, microbiology, botany, pharmacology, biochemistry of cancer, and the immunobiology of AIDS/ARC.
- Directed research of 11 M.S. students.
- Directed research of 10 Ph.D. students.
- Directed research of 4 Post-doctoral students.
- Performed research, have written, and/or presented over 60 research papers, abstracts, and presentations.
- Invited participant in 7 conferences of the Society for Analytical Cytology.
- Received grants and/or contracts from the following:
 - NIH-NCI: Cellular Phosphorus Metabolism.
Cellular Control Mechanisms in Cancer.
Phosphorus Metabolism in Premalignancy.
 - R.A. Welch Foundation: Carcinogenic Hydrocarbon Effect on Nucleic Acids.
 - NASA-MSD: Early Detection of Disease.
Effect of Lunar Material on Plant Cell Cultures.

VERNON E. SCHOLES

Publications, Presentations, Abstracts:

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- Larsen, Scholes, and Skinner, 1974. "Effect of 4-Chloroglutaranilic Acid on Growth and Development of Sunflower Seedling." American Journal of Botany. 61(3):290-295.
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- Baur, Walkinshaw, Scholes, and Venkateswaran, 1971. "Synthesis of Ergastic Material Pine Tissue Cultures." Demonstration, American Society for Cell Biology #676, Journal of Cell Biology, 48:342.
- Rogers, Kimzey, and Scholes, 1971. "Quantitative Distribution of Nucleo-protein of Dividing Cells as Revealed by Ultraviolet Microspectrophotometry." Demonstration, American Society for Cell Biology, #689. Journal of Cell Biology, 48:346.
- Strzinek, Norton, and Scholes, 1971. "Differences in Liver Glyoxalase I from Normal and Cancerous Mice." Abstract #577. Presentation, American Society for Cell Biology. Journal of Cell Biology, 48:293.
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Starkey, Logan, and Scholes, November 1981. "Immune Response Assayed by Flow Cytometry." Oklahoma Academy of Sciences, Enid, Oklahoma.

Starkey, and Scholes, February 1982. "Detection of Bacterial Infection Through Flow Microfluorimetry." Oklahoma Academy of Sciences, Norman, Oklahoma.

Essenberg, Cover, Grover, Hamilton, Richardson, Scholes, and Johnson. Production of 2,7-Dihydroxycadalene and Lacinilene C during the Resistance Response of Cotton to Xanthomonas malvacearum, Beltwide Cotton Prod. - Mech. Conf., Las Vegas, Nevada, January 1982.

Essenberg, Cover, Pierce, Richardson, Scholes, and Hamilton. Local Concentrations of Two Phytoalexins at Sites of Bacterial Colonies in Cotton Leaves, Am. Phytopathol. Soc., Salt Lake City, Utah, August, 1982, Phytopathology, 72, 945.

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Pierce, Cover, Essenberg, and Scholes. Localization of Inhibitory Compounds in Cotton Leaves and Estimation of Their concentrations by Fluorescence Microscopy, 71st Annual Meeting, Oklahoma Academy of Sciences, Chickasha, Oklahoma, November 1982.

Scholes, and Wildman, November 1982. "Effect of Tumors on the Immune Status of the Host. Oklahoma Academy of Science, Chickasha, Oklahoma.

Cochrane, and Scholes, February 1983. "The Effect of Tumor Progression on B-cells and T-cell Subsets." Presented at the Mid-Winter Collegiate Academy Meeting, Oklahoma Academy of Science, Oklahoma State University, Stillwater, Oklahoma.

Manteuffel, and Scholes, February 1983. "Blastogenic Response of Lymphocytes to Specific Tumor Antigens During Tumor Development." Presented at the Mid-Winter Collegiate Academy Meeting, Oklahoma Academy of Science, Oklahoma State University, Stillwater, Oklahoma.

Isaac and Scholes, February 1983. "Effect of Tumor Progression on Phagocytosis." Presented at the Mid-Winter Collegiate Academy Meeting, Oklahoma Academy of Science, Oklahoma State University, Stillwater, Oklahoma.

Wiet and Scholes, February 1983. "Effects of Tumors on Macrophage Migration as Tumors Progress." Presented at the Mid-Winter Collegiate Academy Meeting, Oklahoma Academy of Science, Oklahoma State University, Stillwater, Oklahoma.

Essenberg, Cover, Pierce, Richardson, Scholes, and Hamilton, 1982. "Local Concentrations of Two Phytoalexins at Sites of Bacterial Colonies in Cotton Leaves." Phytopathology, 95 (Abstr.).

Gottlieb, Gottlieb, and Scholes, 1987. "Reconstitution of Immune Function in AIDS/ARC." Concepts in Immunopathology, 4:261-274.

Scholes, 1990. "Clinical Applications of Flow Cytometry." Medical Laboratory Observer, July, pp.54-58.

Essenberg, Pierce, Cover, Hamilton, Scholes, and Richardson, 1992. "A Method for Determining Phytoalexin Concentrations in Fluorescent, Hypersensitively Necrotic Cells in Cotton Leaves." Physiological and Molecular Plant Pathology, 41:101-109.

Essenberg, Pierce, Hamilton, Cover, Scholes, and Richardson, 1992. "Development of Fluorescent, Hypersensitively Necrotic Cells Containing Phytoalexin Adjacent to Colonies of Xanthomonas campestris pv. malvacearum in cotton leaves." Physiological and Molecular Plant Pathology, 41:85-99.

Pierce, Cover, Richardson, Scholes, Essenberg, 1996. "Adequacy of Cellular Phytoalexin Concentrations in Hypersensitively Responding Cotton Leaves." Physiological and Molecular Plant Pathology, 48:305-324.

Special Symposia and Consultantships:

Special Consultant to the United States Department of Agriculture - "Incineration of Virus-Infected Animal Carcasses," 1971.

Consultant in Microbiology - Veterans Administration Hospital, Biloxi, Mississippi, 1975-76.

Special Consultant to the Center for Disease Control, Atlanta, Georgia - "Rapid Identification of Viruses," 1975-76.

Invited Participant, Special Symposium - "Automated Cytology in the Diagnosis of Cancer" - National Institutes of Health, National Cancer Institute, 1975.

Invited Participant, International Symposium - Evaluation of Clinical Laboratory Automation in the Americas, Mexico City, Mexico. Invited speaker - "High Resolution Automated Cytological Screening," 1976.

Local Arrangements Chairman - Association of Medical School Microbiology Chairman Meeting, Mobile, Alabama, 1976.

Program Committee Chairman - Association of Medical School Microbiology Chairman Meeting, 1977-79.

Invited participant - Engineering Foundation Sixth Conference on Automated Cytology, Schloss Elmau, Bavaria, West Germany, 1978.

Invited participant - Engineering Foundation Conference VII on Automated Cytology, Psilomar Conference Grounds, Monterey, California, 1979.

Invited Participant - Conference on Analytical Cytology and Cytometry, Wentworth by the Sea, Portsmouth, New Hampshire, 1981.

Invited Participant - Allergy Symposium at Environmental Ecology Health Center, Dallas, Texas, 1981.

Invited Participant - Allergy Symposium at Environment Ecology Health Center, Dallas, Texas, 1981.

Invited Participant -- Seminar on Flow Cytometry at NASA, Houston, Texas, 1982.

Invited Participant -- Conference on Analytical Cytology and Cytometry - Schloss Elmau, Bavaria, West Germany, 1982.

Director of M.S. Theses:

Earl Meador, 1966 - "Studies of Delayed Hypersensitivity Reactions in Mice"

James Carnes, 1966 - "Phosphorus Metabolism in Atypical Mycobacteria"

James Shaw, 1966 - "Electron Microscopy of Vesicles Present in Bacterial Lysates of Escherichia coli"

- J. Frederick Chapel, 1967 - "The In Vitro Interaction of 3-Methylcholanthrene with Deoxyribonucleic Acid"
- Russell Hollingsworth, 1968 - "Phospholipids of Atypical Mycobacteria"
- Bruce Gunn, 1968 - "Effects of the Soil Conditioner 'Superbio' upon the Cellulose Decomposing Bacteria and the Crop Yield of Soil"
- Joe Abrams, 1970 - "Ultrastructural Changes of Tumor Implants in Mice"
- Robert Pardue, 1972 - "Electron Microscopy of Lymphocytes from Lymphosarcoma Bearing Mice"
- Jon D. Blackley, 1972 - "A Carcinogenic Agent Elaborated by Liver Cells from Lymphosarcoma Bearing Mice"
- Rob Hromas, 1979 - "Immunosuppression Induced by a Murine RNA Tumor Virus Extracted from a Lymphosarcoma"
- Steve Wildman, 1982 - "Effect of a Lymphosarcoma on the Immune Status of the Host"
- Director of Ph.D. Dissertations:
- H. Frederick Chapel, 1969 - "In vivo DNA Modifications by Polycyclic Hydrocarbons"
- Paul Holmgren, 1969 - "The Use of p^{32} and Autoradiography in an Ultrastructural Study of Phosphorus Incorporation in Tissue of the Tumor-bearing Host"
- Tom Rogers, 1979 - "Light and Electron Microscope Studies on the Chemotherapeutic Effect of a Combination of Dimethyl Sulfoxide and Hematoxylin on a Transplantable Lymphosarcoma"
- Robert Strzinek, 1970 - "A Characterization of the Glyoxalase Enzyme from Normal and Tumor Systems"
- William Nunez, 1970 - "A Comparative Study of Passive Transfer Mechanisms of Tuberculin and Chemical contact Delayed Hypersensitiveness in the Guinea Pig"
- Stephen P. Larsen, 1972 - "Effect of 4-Chloroglutaranilic Acid on Growth and Development of Sunflower Seedlings"
- Buford L. Brian, 1972 - "Lipids and Phospholipase Activity of Vibrio Cholerae"
- James E. Carnes, 1972 - "In Vivo and In Vitro Transformation of Mouse Tissues from a Murine Lymphosarcoma"
- Jerri Lindsey, 1972 - "A Study of Normal, Pre-Tumor, and Tumor Cells from Mice Bearing Lymphosarcoma"
- Terri Lindsey, 1972 - "Effect of Tumor Tissue on Mouse Serum Proteins"

Director of Post-Doctoral Work

Tom D. Rogers, Ph.D. NASA-MSC. Early Detection of Disease

1969-72

Paul S. Baur, Jr., Ph.D. NASA-MSC. Effect of Lunar Material on the Ultrastructure of
Plant Cells.

1970-72

Thomas Croley, Ph.D. NASA-MSC. Effect of Lunar Material on the Ultrastructure of
Plant Cells.

1971-72

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1979-80